OPINION ARTICLE

REVISED The convergent epidemiology of tuberculosis and human cytomegalovirus infection [version 2; peer review: 2 approved]

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Abstract

Although several factors are known to increase the risk of tuberculosis, the occurrence of tuberculosis disease in an infected individual is difficult to predict. We hypothesize that active human cytomegalovirus infection due to recent infection, reinfection or reactivation plays an epidemiologically relevant role in the aetiology of tuberculosis by precipitating the progression from latent tuberculosis infection to disease. The most compelling support for this hypothesis comes from the striking similarity in age-sex distribution between the two infections, important because the age-sex pattern of tuberculosis disease progression has not been convincingly explained. Cytomegalovirus infection and tuberculosis have other overlapping risk factors, including poor socio-economic status, solid organ transplantation and, possibly, sexual contact and whole blood transfusion. Although each of these overlaps could be explained by shared underlying risk factors, none of the epidemiological observations refute the hypothesis. If this interaction would play an epidemiologically important role, important opportunities would arise for novel approaches to controlling tuberculosis.

Keywords

Tuberculosis, latent tuberculosis infection, human cytomegalovirus, epidemiology, age pattern, risk factor

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

We have revised the article in accordance with the suggestions made by the reviewers. We have phrased some of the conclusions (with regard to congruent risk factors and CMV vaccination) more cautiously, and added immunological detail on the role of Type I IFN and the effect of human CMV on NK cell function. See detailed responses to the reviewers' comments.

See referee reports

Introduction

With 10.4 million new cases and 1.7 million deaths per year, tuberculosis (TB) remains a major global health problem¹. Only 5%–15% of individuals infected with *Mycobacterium tuberculosis* (Mtb) ever develop TB disease, and over 50% of these do so within two years after infection². Although risk factors for progression to TB disease have been identified³, disease occurrence cannot be accurately predicted⁴.

Recent data suggest that infection with human cytomegalovirus (HCMV) is a predictor of TB disease in infants. In a cohort study of South African infants, an HCMV-specific IFN- γ T-cell response was associated with a 2.2-fold increased risk of TB disease over a period of up to 3 years. A similar response to Epstein-Barr virus (EBV) showed no such associations⁵. HCMV-positive and HCMV-negative infants had distinct immune pathways associated with TB disease. Although CD8⁺ T-cell activation was a distinguishing feature of HCMV-positive infants, the proposed immunological mechanism was impairment of the natural killer (NK) cell response. In African infants, HCMV infection induced profound CD8⁺ T-cell and NK cell differentiation and poor physical growth^{6–7}.

The possibility that this association between HCMV and TB disease progression is causal, also holds in adults, and thus merits further study is dependent on its epidemiological plausibility. Only few published studies have investigated epidemiological associations between the two diseases^{8–10}. Despite this paucity of direct evidence we argue that the epidemiology of TB and HCMV share important similarities that make HCMV infection a plausible candidate as a cause of TB disease progression.

Viral triggers of tuberculosis disease

Various etiological frameworks for TB disease progression have been developed. One proposed by Comstock considers TB disease the result of two hits or causes, one of which is Mtb infection, and the other (still) unknown¹¹. In this framework, factors that strongly increase the risk of TB disease such as HIV infection or anti-tumour necrosis alpha therapy may act as a second hit but would not account for all or most TB cases.

Several factors have been identified that increase the risk of disease progression, such as low body-mass index¹², diabetes¹³, tobacco smoking¹⁴, and alcohol abuse¹⁵. As their effects are modest another framework has emerged that these are *predisposing*

conditions for disease progression while other, yet unidentified *precipitating events* are needed to trigger progression to active disease¹⁶. Among the precipitating events suggested are viral infections, possibly through induction of Type I interferons (IFN). Elevated Type I IFN signalling is a hallmark of viral control, however, Type I IFN is also associated with susceptibility to bacterial infections, including Mtb^{17–22}. The Type I IFN response is tightly regulated by prostaglandins and the balance between prostaglandins PGE2 and LXA4 can be manipulated by Mtb to drive Type I IFN mediated necrosis and promote mycobacterial dissemination^{19,23}. Type I IFN-associated impairment of the immunity against Mtb has been shown for influenza A²¹. A role for influenza A infection has also been suggested by epidemiological data. Notification of TB tends to peak in the months after winter when most respiratory viruses circulate²⁴, and TB mortality has shown increases during influenza epidemics^{25,26}. However, careful analysis of seasonality data suggests that it is TB transmission rather than disease progression that is increased in winter²⁷, and increased TB mortality during influenza epidemics may reflect increased case fatality among TB patients due to secondary influenza rather than increased TB incidence.

As with many viral infections, Type I IFN can control HCMV replication^{28,29}. HCMV has been suggested in three studies from Nigeria, Russia and Uganda that all found higher prevalence or levels of IgG HCMV antibodies in diagnosed TB patients compared to healthy controls and patients diagnosed with other diseases^{8–10}.

Human cytomegalovirus infection

HCMV, human herpesvirus 5, is a double-stranded DNA virus. After primary infection, usually through mucosal contact, HCMV remains dormant in the host's myeloid tissues but can reactivate if immunity is compromised. Primary infection is often asymptomatic but can present as mononucleosis with fever, pharyngo-tonsillitis and lymphadenopathy. In congenitally infected infants HCMV may cause severe generalized infection with high case fatality and neurologic sequelae³⁰. Generalized infection also occurs in severely immunocompromised adults, usually through reactivation. During primary infection and reactivation virus is shed in the urine, saliva, breast milk, cervical fluid and semen³¹. Common routes of transmission are from mother to child during delivery, between children and by sexual contact. Transmission through blood transfusion and solid organ transplantations also occurs.

HCMV viruses show genomic diversity, in particular in genes coding for envelope glycoproteins, and polymorphisms in these genes have been used to genotype strains^{32,33}. Both immunocompromised and immunocompetent individuals can be re-infected and harbour multiple HCMV strains^{34–36}.

Primary HCMV infection is characterized by profound expansion of antigen specific CD8⁺ and CD4⁺ T cells and NK cell populations with specificity for HCMV³⁷. HCMV expanded NK cells can display inappropriate homing to tissue infected with other pathogens and lower IFN- γ secretion in response to pathogens³⁸. HCMV infection drives the expansion of

CD94/NKG2C NK cells and these cells are important for control of viral replication³⁹. In HCMV positive infants who progressed to TB disease in the South African cohort there was lower expression of CD94 and NKG2C (KLRD1 and KLRC3) transcripts and lower frequency of NK cells⁵. The NKG2C receptor is encoded by the *KLRC2* gene which is deleted in approximately 10% of individuals⁴⁰. The *KLRC2* gene deletion is associated with lower numbers of mature NK cells and increased risk of HIV infection and disease progression^{41,42}, as well as with susceptibility to autoimmune conditions and cancer⁴⁰. Susceptibility to TB in this infant population may be due to loss of control of CMV infection due to *KLRC2* gene defects in some individuals.

HCMV has multiple immune evasion strategies³⁷, which may make the microenvironment around latently infected myeloid cells suppressive to T-cell function, potentially creating an environment permissive for mycobacterial growth^{43,44}. This may be through effects of HCMV on the systemic immune response, but also through local effects. The lung is a reservoir of HCMV infection^{45,46} and frequently the site of viral reactivation⁴⁷, which drives inflammation and in mice may cause pulmonary fibrosis⁴⁸. It is therefore possible that active HCMV (re)infection or reactivation of latent HCMV could precipitate progression to TB disease.

Epidemiological convergence

Both *Mtb* and HCMV infections are ubiquitous^{1,49}, and during millions of years of co-evolution have become highly human host-specific^{50–52}. An animal reservoir has been described for neither *Mtb* nor HCMV (several monkey and rodent species have their distinct CMV species), implying that their epidemiological patterns are entirely determined by transmission between, and carriage by, humans.

We hypothesize that immunologically active HCMV infection, whether primary, reactivation or re-infection, acts as (depending on one's preferred framework) second-hit or precipitating factor for progression of latent TB infection to TB disease at an epidemiologically relevant scale. We base this on two arguments: their striking similarity in age distribution, and the existence of congruent risk factors [Box 1].

Box 1. Approach to evidence gathering

We systematically searched PubMed for the following combinations of keywords: tuberculosis and cytomegalovirus; cytomegalovirus and prevalence or seroprevalence; cytomegalovirus and age; cytomegalovirus and reinfection; cytomegalovirus and sexual; tuberculosis and sexual; tuberculosis and sexual transmitted infections or Chlamydia or gonorrhoea or human papillomavirus; tuberculosis and blood transfusion; cytomegalovirus and blood transfusion; tuberculosis and gastrectomy; cytomegalovirus and renal dialysis; tuberculosis and renal dialysis; tuberculosis and organ transplantation; cytomegalovirus and organ transplantation.

We in addition made use of an extensive review of the literature on age-sex distribution of tuberculosis incidence published by Nagelkerke (2012)⁵³.

Age distribution

The probability of progressing from TB infection to disease has a highly typical age distribution. The classical description of this age pattern is by Comstock *et al.*, who followed 82,269 Puerto Rican children reacting to tuberculin enrolled in 1949–1951 for 8 to 20 years [Figure 1]⁵⁴. This pattern, confirmed in a systematic review of studies from the pre-chemotherapy era⁵⁵, is defined by a peak in the first 1–4 years of life, followed by a trough until early puberty, rising to a second peak around the age of 20 years. Analyses of notification and prevalence data from high-incidence countries show that incidence starts to rise again from the sixth decade^{56,57}. Although several explanations for this age pattern have been suggested, none has been proven.

Infants. Studies from the pre-chemotherapy era showed that, while the risk of infection with *Mtb* in the first year of life was over 10-fold lower than later in childhood, the risk of progression to disease once infected was much higher with up to 50% of infected infants developing disease⁵⁵. These high progression rates have been attributed to age-specific maturation of immune responses⁵⁸, although the mechanisms responsible for this vulnerability have not been elucidated⁵⁹.

HCMV infection in infants is common⁶⁰. Depending on the country and socio-economic status of the mother, between 10 and 60% of children are HCMV IgG seropositive (reflecting current or past active infection) by the age of 12–36 months^{61–68}. Important causes are congenital infection and transmission through breastfeeding; >85% of HCMV seropositive women excrete virus in the breastmilk^{60,69–72}. Infants infected through breastfeeding do not develop disease, probably due to protection by maternal antibodies, but do shed virus in saliva and urine intermittently for months, by which they may transmit HCMV to other children and caregivers^{31,60,64,73}. Shedding of HCMV shows a steep decline by the age of 5 years³¹, coinciding with the age at which TB incidences drop^{54,55}.

Figure 1. Age-specific incidence of tuberculosis disease among tuberculin-reactive children. Average annual rate of tuberculosis disease in a cohort of 82,269 Puerto Rican children with a positive tuberculin skin test, by age of disease occurrence. Children were enrolled in the period 1949–1951, and followed for 8 to 20 years. Figure reproduced with permission from Comstock *et al.* (1974)⁵⁴.

Adolescents. The rate of progression to TB disease then remains low until puberty. Several studies have observed an increase in TB incidence from this age onward among children who were exposed to infectious TB patients or had a positive tuberculin response, leading to a peak in incidence in the first half of the third decade^{54,74–79}. This phenomenon has been attributed to hormonal changes, but again without a putative mechanistic pathway⁸⁰.

Most population-based studies of HCMV seroprevalence show exactly this age pattern: a slow increase in HCMV IgG seroprevalence up to the age of 10–15 years, followed by an acceleration during adolescence^{61,63–66,68,81–88}. One explanation for this increase in seroprevalence is sexual transmission. Various studies found that HCMV conversion among women was associated with sexual activity^{89–93}. However, as several studies of adolescents found no association of HCMV seroprevalence with sexual exposure^{83,94,95}, other transmission routes such as mouth-to-mouth kissing may also be important.

Another indication that HCMV infection may be implicated is the sex difference in TB disease progression in the second decade. For girls the increase in TB incidence starts 2–4 years earlier than for boys, and progression rates tend to remain higher in women than in men for the subsequent two decades, a pattern that was observed before the HIV era in various populations^{54,75,76,78,79,96–99}. This pattern is again reflected in that of HCMV infection. The acceleration of HCMV seroprevalence during puberty and adolescence is steeper in girls than in boys and is higher in women of childbearing age than in men in populations with relatively low HCMV seroprevalence^{49,64,65,84,100–102}. Age-adjusted HCMV seroprevalence does not differ between men and women in populations with high seroprevalence^{49,103}. This may be because IgG seroprevalence measures cumulative infection experience and thus ignores reinfection. HCMV reinfection, identified by DNA typing or strain-specific antibody responses, is a common occurrence in sexually exposed women^{104–106}.

Elderly. Although there is little data on TB progression rates in the elderly, age patterns of TB notifications suggest increased progression rates from the sixth decade onward^{1,56}. In populations with declining incidence rates over the past decades this is partially a cohort effect, whereby younger generations have lower prevalence of latent infection^{107,108}. However in high-incidence countries with little change in TB incidence, notification rates clearly increase at older age¹. This is also observed for TB prevalence in population surveys, suggesting that this is not explained by better access to diagnosis¹. HCMV infection has been implicated as a cause of age-related decrease in naïve T cells and increase in memory T cells known as immunosenescence¹⁰⁹. However, reactivation of HCMV infection is also common at old age, probably reflecting weakening immune control³⁷. Detection of viral DNA increases after the age of 60–70 years^{110,111}, and viral DNA is frequently detected in urine and plasma of elderly people^{112,113}.

Congruent risk factors

Our hypothesis predicts that factors that drive CMV (re-)infection are also risk factors for TB. We highlight the four most important: socio-economic status, sexual contact, blood transfusion, and solid organ transplantation.

Socio-economic status. Incidence and prevalence of CMV infection are associated with poor socio-economic status (SES), between countries as well as within countries and communities^{49,64,65,100,114–116}. This includes association with crowding, in particular the number of young children in household^{117–119}. Several studies found ethnicity or migrant status to be independently associated with age-adjusted CMV prevalence^{65,84,120}, which may partly reflect higher background infection rates in the country of origin. In a US study the association with ethnicity was explained by differences in exposure to infants and sexual risk⁹³.

Also the incidence of TB, often regarded as the archetypal poverty disease, shows a remarkable inverse gradient with SES at the household, regional and country level^{121–123}. This association has been explained mainly by crowding in ill-ventilated spaces conducive to Mtb transmission¹²⁴, poor nutritional status^{12,125}, alcohol abuse¹⁵ and, possibly, indoor air pollution¹²⁶. Similarly, in low-incidence countries, TB incidences are higher in particular ethnic groups and immigrants^{127,128}, which also may reflect socio-economic disparities and differences in background infection rates¹²⁹. Very few studies have attempted to investigate whether these and other known risk factors explain all of the observed variation in SES-related TB incidence¹³⁰.

Sexual contact. The risk of CMV (re-)infection in adults is correlated with measures of sexual activity such as age at first intercourse, recent and lifetime number of sexual partners and condom use, as well as with prevalence of other sexually transmitted infections^{89,90,92,131–133}. Historically, TB has also been associated with sexual promiscuity in medical and popular literature (reviewed in 53) but no systematic epidemiological data exist. Investigation of associations between TB disease and sexually transmitted infections has been strongly dominated by HIV infection, which may obviously be a major confounder. There have been few studies from low HIV prevalence populations. One from China found an association between history of TB and human papilloma virus infection¹³⁴.

Interestingly, the declining TB mortality rates in The Netherlands and England and Wales in the 20th century showed no surge during the Great Depression^{121,135}, when SES status deteriorated thereby affecting several of these known risk factors, in particular nutritional status. They did however surge during and shortly after the Second World War^{121,135}. In England and Wales this was not paralleled by major deterioration in nutritional status; in The Netherlands famine only started in the winter of 1944–45 while the increase in TB mortality started already from 1942⁵³. In both countries during this

period major increases were seen in sexually transmitted infections, mainly related to presence of large numbers of Allied and Axis troops⁵³.

Blood transfusion. Transfusion-associated CMV infection occurs in particular following multiple transfusions of whole blood or granulocytes, and can be prevented by removal of white blood cells^{136–138}. Increased incidences of TB have indeed been described in two categories of patients who in the past often received multiple whole blood transfusions: patients who underwent (partial) gastrectomy, mainly for bleeding gastric ulcers^{139,140}, and patients with end-stage renal disease on haemodialysis¹⁴¹. For both these categories alternative explanations for increased TB incidences are possible: low body mass index for gastrectomy^{139,140}, and impaired cellular immunity due to uraemia for haemodialysis¹⁴². Nonetheless, several studies among haemodialysis patients have suggested increased rates of CMV (re)infection, either or not associated with transfusion of blood or blood products^{143–147}, as well as increased rates of CMV reactivation¹⁴³.

Solid organ transplantation. The incidence of symptomatic CMV infection is strongly increased in solid organ transplant patients, mainly due to infection from a CMV IgG positive donor¹⁴⁸. Solid organ transplantation also increases the risk of TB disease^{141,149–151}. TB incidence is highest in lung transplant patients and associated with presence of latent TB infection, clinical condition and intensity of the immunosuppressive therapy; the latter has been brought forward as the sole explanation for the increased TB risk¹⁵². Interestingly, a study among Korean solid organ transplant patients found that the risk of developing TB was associated with CMV infection within the prior 3 months¹⁵³.

Potential impact on tuberculosis control and elimination

If indeed CMV (re-)infection or reactivation commonly precipitates progression from latent infection to active TB, this will suggest novel approaches to TB control. Combining a test for Mtb infection with one for ongoing or recent active CMV infection may strongly increase our ability to predict the development of TB disease and allow the targeting of preventive treatment to those most at risk⁴. Vaccination against CMV might prevent TB in those with TB infection. A wide range of CMV vaccines are currently in clinical development including

plasmid-based vaccines, viral vector vaccines, attenuated HCMV strains, and recombinant protein and peptide vaccines¹⁵⁴. Recently, a genetically modified CMV vector expressing antigens from Mtb (RhCMV/TB) has shown some protection against Mtb in a non-human primate study¹⁵⁵. If the human version of this vaccine was able to afford (partial) protection against CMV, it could also significantly impact the TB epidemic. However, there is currently no widely available HCMV vaccine and it is unclear if vaccines based on HCMV in humans will offer similar protection to those based on RhCMV in non-human primates. Since CMV infection may also affect TB treatment response, another potential application therefore could be the provision of CMV antiviral treatment as an adjunct to TB treatment, for example of patients with multidrug resistance.

Future research

There is an urgent need for elucidating the role of CMV infection in TB disease progression. Further serological and cellular studies should be done to confirm the association between TB disease and CMV infection. However, in settings with high CMV seroprevalence (also those with highest TB incidence) it will be important to identify recent reinfection for which various diagnostic approaches exist³⁰. Their relative merits are beyond the scope of this article, but some may potentially signal reactivation due to Mtb replication, i.e. consequence rather than cause. Therefore, ultimately longitudinal studies are needed in which the incidence of TB disease among those with latent TB infection is measured over time comparing those with CMV (re-)infection or reactivation to those without. These studies should be supplemented with immunological studies to define the mechanisms through which CMV precipitates progression to active TB disease. Finally, it will be important to study the role of CMV reactivation during TB disease and its effect on the response to TB treatment.

Data availability

No data is associated with this article.

Competing interests

No competing interests were disclosed.

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Maziar Divangahi

McGill International TB Center, University of McGill, Montréal, QC, Canada

The authors effectively addressed all my concerns.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB Immunologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 22 March 2018

<https://doi.org/10.5256/f1000research.15429.r32121>

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Maziar Divangahi

McGill International TB Center, University of McGill, Montréal, QC, Canada

Our continuous exposure to a multitude of pathogens requires a greater understanding of the host response to heterologous infections and is fundamental for developing novel therapies and vaccines against infectious diseases. In line with this, heterologous immunity to viruses and bacteria is an extremely complex scenario as our immune response greatly differs upon viral

versus bacterial infection. Thus, how our immune system makes a balanced response to control both viral and bacterial infections without killing the host is a fascinating area of research.

In this review article, Cobelens and colleagues reviewed the available epidemiological data for human cytomegalovirus (HCMV) and *Mycobacterium tuberculosis* (*Mtb*) infections. The review is well written and provides interesting human observations that HCMV may contribute to the progression of latent TB to active disease. However, I have three major comments that potentially can improve the conceptual idea of the current review.

1) Type I IFN is a chief antiviral cytokine, which also plays a critical role in immunity to CMV infection (*Plos Pathogens*, 10:e1003962, 2014). However, it has been well documented that type I IFN increases host susceptibility to some bacterial infections including *Francisella tularensis* (*J. Immunol.* 169, 1665-1668, 2002), *Listeria monocytogenes* (*J. Exp. Med.* 185:921, 1997) and *Mtb* (*J. Interferon Cytokine Res.* 25:694, 2005 & *Nature*, 511:99, 2014). This concept has been also supported by another recent study (JID, 290:270 2014) demonstrating influenza infection increased susceptibility to *Mtb* infection in a Type I IFN dependent manner. Although the authors briefly mention this idea, a cohesive expansion of this concept would provide further insight for the important role of type I IFN in viral infection and susceptibility to *Mtb* (*Trends in Immunology*, 36:307, 2015).

2) The authors need to be cautious about their conclusions regarding a recent paper using nonhuman primate (rhesus macaques) cytomegalovirus vectors encoding *Mtb* antigens (RhCMV/MTB) (*Nature Medicine*, 24:130, 2018) for the vaccine in TB. Although the protective data from this study are very impressive, the lack of cellular mechanism (e.g. the protection was independent of effector T cells) as well as the lack of several important controls including the empty vector (RhCMV) indicate that further investigations are required to have a better understanding of this approach as a vaccine in pre-clinical study prior to any human trial for TB.

3) The presented human observations that sexual contact and whole blood transfusion are the risk factors for tuberculosis is very speculative. Thus, the author should consider rephrasing this section at least in the abstract as it sounds very confirmative.

Minor comments:

1) The Age-specific death rates from TB in England and Wales was also reported for 1913 and 1918 that shows the same pattern (Table 2) and the authors may want to include this reference:

Langford, C. The age pattern of mortality in the 1918–1919 influenza pandemic: an attempted explanation based on data for England and Wales. *Med. Hist.* 46, 1–20 (2002).

2) As there is no evidence of *Mtb* activating latent HCMV in the lungs (Page 3), which is also not the focus of this review, the author may want to consider removing this entire paragraph.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Partly

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB Immunologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Apr 2018

Frank Cobelens, Department of Global Health and Amsterdam Institute for Global Health and Development, Academic Medical Center, Meibergdreef 9, AZ, The Netherlands

We thank Dr. Divangahi for his valuable comments.

Here we respond point-by-point, referring to the revised version of our paper.

Major comments

1: "(...) Although the authors briefly mention this idea, a cohesive expansion of this concept would provide further insight for the important role of type I IFN in viral infection and susceptibility to Mtb".

Response: The reviewer is right to point out that Type I IFN plays a role in HCMV infection as well as in Mtb infection. We expanded the paragraph on viral triggers to include more detail on the possible role of Type I IFN.

2. "The authors need to be cautious about their conclusions regarding a recent paper using nonhuman primate (rhesus macaques) cytomegalovirus vectors encoding Mtb antigens (RhCMV/MTB) (Nature Medicine, 24:130, 2018) for the vaccine in TB. (...)"

Response: We agree with this criticism and now phrased this more cautiously by pointing out that there is currently no widely available HCMV vaccine and it is unclear if vaccines based on HCMV in humans will offer similar protection to those based on RhCMV in non-human primates.

3. "The presented human observations that sexual contact and whole blood transfusion are the risk factors for tuberculosis is very speculative. Thus, the author should consider

rephrasing this section at least in the abstract as it sounds very confirmative."

Response: We agree that for these two risk factors the evidence base is limited, although we do point out reasons why (e.g. the confounding effect between TB and sexual contact by HIV status). We rephrased this statement in the abstract as "(...) including poor socio-economic status, solid organ transplantation and, possibly, sexual contact and whole blood transfusion."

Minor comments

1. "The age-specific death rates from TB in England and Wales was also reported for 1913 and 1918 that shows the same pattern (Table 2) and the authors may want to include this reference:

Langford, C. The age pattern of mortality in the 1918–1919 influenza pandemic: an attempted explanation based on data for England and Wales. *Med. Hist.* 46, 1–20 (2002)."

Response: Indeed TB mortality showed a peak in 1918 in England and Wales, as it did in Switzerland and South Africa (as referenced), as well as in other countries such as The Netherlands (not referenced). This mortality peak has generally been associated with the Spanish Flu epidemic rather than with WW-I, among other because several of these countries were not involved in the war. We feel that this point is rather secondary to our reasoning and does not need additional referencing. Note that mortality peak in 1913 observed by Langford in in England and Wales was observed only in the age group 0-4 years, with little bearing on overall mortality.

In light of this discussion we feel it is important to point out that increased TB mortality during influenza epidemics may reflect increased case fatality among TB patients due to secondary influenza rather than increased TB incidence. We now added this consideration to the paragraph on viral triggers of TB.

2. "As there is no evidence of Mtb activating latent HCMV in the lungs (Page 3), which is also not the focus of this review, the author may want to consider removing this entire paragraph."

Response: We agree that this aspect is outside the focus of our review and took out the part of the sentence related to Mtb infection reactivating HCMV infection. We did leave in the remainder of the paragraph but did include a statement that the effect of HCMV on the immunity to Mtb may be systematic as well as local, i.e. in the lungs.

Competing Interests: Apart from being the article's first author I have no competing interests to disclose.

Reviewer Report 14 March 2018

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Blair L. Strang

Institute for Infection and Immunity, St George's, University of London, London, UK

The interaction of different pathogens in an infected individual is a fascinating subject, but, in general, poorly understood. For the most part, it is thought that infection with one pathogen facilitates the replication and pathogenesis of another. An example of this is the clear and long standing link between human immunodeficiency virus (HIV) infection and development of severe disease related to MTB mycobacterium tuberculosis (MTB) infection. What is interesting of MTB infection are the concepts of predisposing or preexisting infection other than HIV linked to MTB (for example, the widespread respiratory pathogen influenza.)

In this article, the authors outline intriguing lines of converging evidence detailing the possible association of human cytomegalovirus (HCMV) and MTB infection, suggesting that HCMV infection is a relevant factor in the incidence of MTB disease.

The evidence presented rests largely on epidemiological findings involving age distribution and congruent risk factors. There is an interesting link between the incidence of MTB in early life and adolescence that mirrors acquisition of HCMV either during pregnancy/post partum or by sexual contact in adolescence. Several congruent risk factors are discussed. However, the authors concede that these factors could be applicable to many widespread opportunistic pathogens, including HCMV.

Overall, the argument presented based on epidemiological evidence is compelling and the possible link between HCMV and MTB infection should be investigated further. Indeed, the authors should have done more to highlight very recent work from one of their laboratories on this topic. This study, mentioned in the opening paragraphs, shows a clear association of the presence of T cells recognizing HCMV and an increased risk of MTB disease early in life. What is especially interesting about this study is the possibility that development of MTB disease is related to the impairment of NK cell function. Much recent work in HCMV pathogenesis by Wilkinson and colleagues has highlighted the many and diverse mechanisms that HCMV employs to evade NK cells. It is interesting to consider that HCMV evasion of the immune response to infection is directly related to development of MTB disease.

Other points surrounding mechanisms linking HCMV and MTB infection are also unclear. The authors mention that the lung may be a reservoir for HCMV. However, this is based on studies in mice using murine cytomegalovirus (MCMV). The pathology of MCMV does not accurately mirror that of HCMV. Thus, more compelling evidence relating the presence of HCMV in the lung with disease must be presented. Based on the data discussed above, co-incident infection of HCMV and MTB in lung tissue may not be required for disease, but, perhaps, modulation of the immune system.

Finally, the authors consider therapeutic intervention. They highlight the sterling work of Picker and colleagues using rhesus cytomegalovirus (RhCMV) as a vaccine vector. These studies have shown that in non-human primates a RhCMV-MTB vaccine candidate can offer notable protection against challenge with MTB. It must be noted, however, that there is currently no widely available HCMV vaccine and it is unclear if vaccines based on HCMV in humans will offer similar protection to those based on RhCMV in non-human primates. It may be some time before viable HCMV based vaccines are available. In the short term it may be better to peruse the other suggestion the

authors make, which is to trial the use of anti-HCMV drugs in patients with MTB.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 22 Apr 2018

Frank Cobelens, Department of Global Health and Amsterdam Institute for Global Health and Development, Academic Medical Center, Meibergdreef 9, AZ, The Netherlands

We thank Dr. Strang for his valuable comments.

Here we respond point-by-point, referring to the revised version of our paper.

1. "(...)Indeed, the authors should have done more to highlight very recent work from one of their laboratories on this topic. This study, mentioned in the opening paragraphs, shows a clear association of the presence of T cells recognizing HCMV and an increased risk of MTB disease early in life. What is especially interesting about this study is the possibility that development of MTB disease is related to the impairment of NK cell function. Much recent work in HCMV pathogenesis by Wilkinson and colleagues has highlighted the many and diverse mechanisms that HCMV employs to evade NK cells. It is interesting to consider that HCMV evasion of the immune response to infection is directly related to development of MTB disease."

Response: We agree that the possible role of impairment of NK cell function deserves more attention. We now elaborate on this aspect in the section entitled "Human Cytomegalovirus Infection".

2. "The authors mention that the lung may be a reservoir for HCMV. However, this is based on studies in mice using murine cytomegalovirus (MCMV). The pathology of MCMV does not accurately mirror that of HCMV. Thus, more compelling evidence relating the presence of HCMV in the lung with disease must be presented. Based on the data discussed above, co-incident infection of HCMV and MTB in lung tissue may not be required for disease, but,

perhaps, modulation of the immune system."

Response: We added the following references: Gordon et al, J Exp Med 2017 (a study of donor organs that showed the lung is a major site for CMV DNA) and Poole et al. J Infect Dis 2015 (that found CMV in alveolar macrophages). But it is also true that CMV may not need to be present in the lung as it impacts the systemic immune response and therefore has an indirect effect still relevant for lung immunity. It is possible that both co-infection of lung AND CMV impact on systemic immune response contribute to TB risk in the CMV infected individual. We added this consideration to the in the section entitled "Human Cytomegalovirus Infection".

3. "It must be noted, however, that there is currently no widely available HCMV vaccine and it is unclear if vaccines based on HCMV in humans will offer similar protection to those based on RhCMV in non-human primates."

Response: We agree with this caveat that we added to the text.

Competing Interests: Apart from being the article's first author I have no competing interests to disclose.

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